Journal of Surgical Oncology 64:74–78 (1997)

Pituitary Adenoma and Bilateral Male Breast Cancer: An Unusual Association

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An unusual case is presented of bilateral breast cancer in a male patient with a long history of endocrine dysfunction due to a prolactinoma. The role of abnormal endocrine function in the development of male breast cancer is reviewed. The strongest association between aberrant endocrine function and male breast cancer occurs in patients with Klinefelter's syndrome, who have an approximate 3% lifetime risk of developing breast cancer. Retrospective case-control studies indicate that both estrogen excess and androgen deficiency may be involved in male breast cancer. Clinical studies of estrogen, androgen, and prolactin levels in male breast cancer patients have yielded conflicting results, and the precise nature of the hormonal mechanisms involved in the development of male breast cancer remains to be defined. J. Surg. Oncol. 64:74–78 © 1997 Wiley-Liss, Inc.

KEY WORDS: prolactinoma; androgen; estrogen; male breast cancer

INTRODUCTION

Breast cancer is an uncommon malignancy in men. Approximately 1,400 new cases are diagnosed each year in the United States, compared to 184,000 new cases in women [1]. The frequency of bilateral disease in men is less than in women, and in one reported series it occurred in only 1.4% of male patients [2]. We report the case of a 70-year-old male who developed bilateral carcinoma of the breast 7 years after undergoing surgery for a pituitary prolactinoma and discuss the possible role of aberrant endocrine function in the development of male breast cancer.

To our knowledge there have been only two other case reports of male breast cancer in the setting of a prolactinoma [3,4]. In one reported case, the patient underwent surgery and received post-operative radiation for a pituitary tumor, described as a chromophobic adenoma, at age 22 [3]. Subsequent immunohistochemical stains done on the original paraffin-embedded tumor were consistent with a prolactinoma. Twenty-six years later, carcinoma of the left breast was diagnosed and surgically removed. Eleven years following the surgery on the left breast, a second primary carcinoma of the right breast was surgically removed. In the second reported case, a 68-year-old male presented with carcinoma of the left breast [4]. Hormonal tests revealed a very high serum prolactin level, and a CT scan of the brain showed a large pituitary tumor. The patient underwent a modified radical mastectomy and was given bromocriptine for the pituitary prolactinoma.

CASE REPORT

Our patient was a 70-year-old male who sought medical attention in 1993 for small, firm bilateral breast

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Accepted 15 August 1996.

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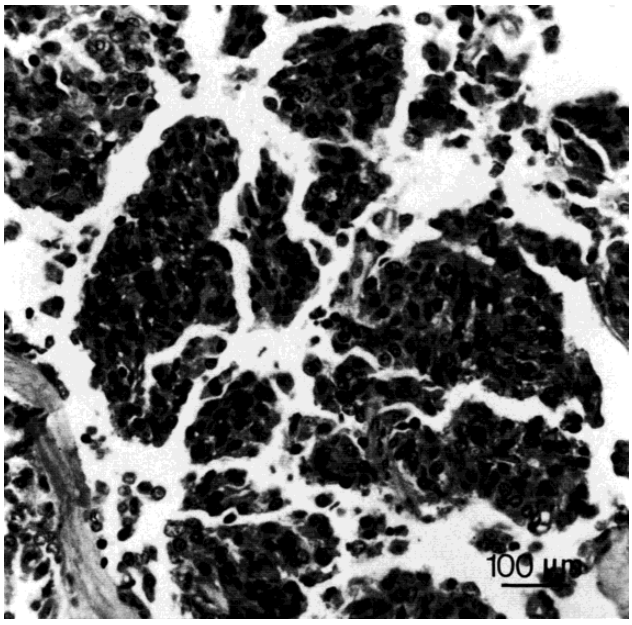

Fig. 1. Pituitary prolactinoma, 1985 (hematoxylin and eosin, original magnification ×100). Antiprolactin antibody immunohistochemical staining was positive.

masses, which had been present and growing slowly for nearly a year. He denied breast pain or skin changes and had no systemic complaints. His past medical history was remarkable for the incomplete development of testosterone-dependent, secondary sexual characteristics and infertility. The patient and his wife tried unsuccessfully to conceive a child for 10 years, but eventually adopted two children. In his midforties he developed galactorrhea and underwent bilateral nipple resections. He was hospitalized at a local public hospital where retrieval of laboratory studies done during this time (i.e., prolactin, testosterone, etc.) was not possible. Pathology showed no evidence of malignant disease. In his late fifties, he became impotent.

In 1985 at age 63, he was found to have an elevated prolactin level, and a CT scan of the brain revealed a large pituitary mass extending into the suprasellar area. There was no history of headache, nausea, or visual field defects. Gynecomastia was present bilaterally and his testicles appeared atrophied. Serum prolactin level was 1,800 ng/ml and serum testosterone was 60 ng/dl. He underwent partial resection of the mass using a transphenoidal approach. The mass was found to be a benign pituitary adenoma, with immunohistochemical staining positive for prolactin (Fig. 1). The patient recovered from his surgery uneventfully and received 5,040 cGy of radiation to the tumor bed.

At presentation in 1993, physical examination revealed a moderately obese 70-year-old male. Head and neck examination was unremarkable. There was no palpable cervical, supraclavicular, or axillary adenopathy. Gynecomastia was no longer present. A 2.0 × 3.0 cm firm, nontender left breast mass was palpated just medial to the nipple scar. Another 1.0 cm mass was palpated medial to the nipple scar on the right breast. Heart and lung examination was normal. The abdomen was obese, soft, and nontender. There were no palpable masses or hepatosplenomegaly. Genitalia examination revealed atrophied, descended testicles bilaterally. Rectal and neurologic examinations were normal. There were no visual field defects. Routine laboratory studies, including a complete blood count and liver function tests, were normal.

An excisional biopsy of the left breast lesion showed infiltrating ductal carcinoma (Fig. 2a). A bone scan showed no evidence of metastatic disease. The patient underwent a left modified radical mastectomy. Frozen sectioned tissue from the right breast mass was also positive for carcinoma, and the same procedure was performed on the right. Pathology showed a 2.0 × 2.5 cm, nuclear grade II, infiltrating ductal carcinoma of the left breast and a 1.5 × 1.9 cm, grade III, infiltrating ductal carcinoma of the right breast (Fig. 2b). One of the 15 left axillary nodes was positive for tumor, none of seven nodes on the right showed evidence of metastatic cancer. Both tumors were estrogen and progesterone receptor positive (estrogen receptor 112.1 fm/mg, progesterone receptor 22.5 fm/mg). The patient recovered uneventfully from his surgery and was placed on tamoxifen. He did well for 6 months, but subsequently developed liver and pulmonary metastases and rapidly declined. An autopsy was not permitted.

To rule out the possibility of Klinefelter's syndrome in our patient, the following analysis was performed. Free nuclei from paraffin-embedded left and right breast tumor tissues were prepared as described by Lee et al. [5]. The suspension was spread on slides and air dried. The nuclei were hybridized simultaneously with SpectrumGreen-labelled, X chromosome-specific alpha satellite DNA and SpectrumOrange-labelled, Y-specific satellite III DNA probes from Vysis according to the protocol provided by the manufacturer. X and Y specific signals were counted on a Jena microscope equipped with Vysis single-bandpass filter sets optimized for viewing SpectrumOrange and SpectrumGreen. One X- and Y-specific signal were observed in the 300 nuclei and analyzed from each specimen. These findings prove that our patient did not have Klinefelter's syndrome.

DISCUSSION

This patient's history of incomplete secondary sexual development, infertility, galactorrhea, and impotence

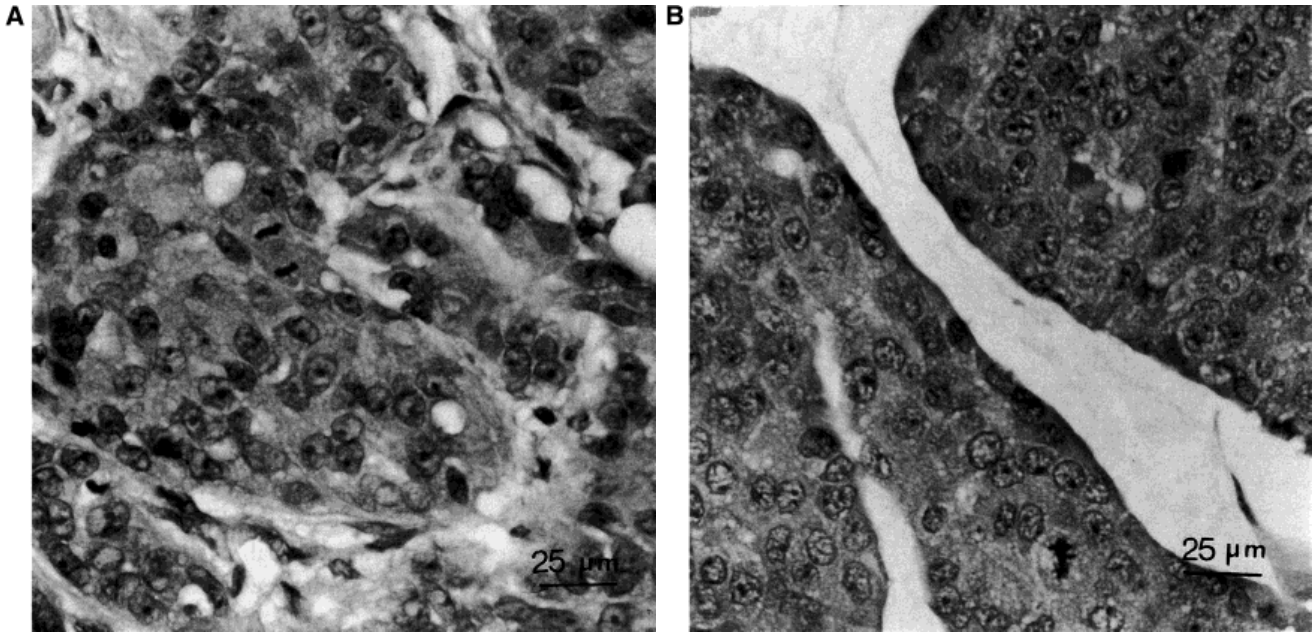

Fig. 2. Infiltrating ductal carcinoma of the left (**a**) and right (**b**) breast (hematoxylin and eosin stem, original magnification ×400).

suggests that he had a functioning prolactinoma present for many years before it was diagnosed. If present at puberty, elevated prolactin levels would, by negative feedback on the pituitary, have resulted in decreased levels of gonadotropic hormones (FSH and LH) and insufficient testosterone to produce fully mature secondary sexual characteristics [6]. Decreased levels of androgen also would account for the patient's subsequent difficulties with infertility and impotence.

The growth of breast tissue in both sexes is mediated by the relative activities of estrogen and androgen. In men, epidemiologic data suggest that states of relative estrogen excess or androgen deficiency play a role in two pathologic conditions of the breast: gynecomastia, a common benign condition, and male breast cancer, a rare malignancy.

Gynecomastia results from the proliferation of the normal rudiments of glandular epithelium present in the male breast. The prevalence among adult patients in several studies has ranged from 32% to 65%, depending on the criteria used to define gynecomastia and the population studied [7]. Approximately 50% of all cases of gynecomastia are either idiopathic or are associated with puberty. The remaining cases are associated with drugs (10–20%), cirrhosis or malnutrition (8%), primary hypogonadism (8%), and a variety of less frequent conditions, including testicular tumors, secondary hypogonadism, hyperthyroidism and renal disease [7]. Alterations in endogenous estrogen or androgen have been found in patients with gynecomastia in association with medications, adrenal, and testicular neoplasms, Klinefelter's syndrome, thyrotoxicosis, cirrhosis, primary hypogonadism, malnutrition, and aging [7]. Case-control studies document that a history of gynecomastia is associated with a sixfold increased risk for male breast cancer [8]. Nonetheless, because gynecomastia is common and male breast cancer is rare, patients with gynecomastia rarely develop breast cancer.

Among men with gynecomastia, a significant risk of developing breast cancer exists only in those with Klinefelter's syndrome, whose lifetime risk approximates 3% [2,8]. Klinefelter's syndrome is characterized by an X, X, Y genotype, gynecomastia, short stature, hypogonadism, and infertility. Plasma testosterone levels are approximately half of normal, and FSH and LH levels are elevated. The cytogenetic evaluation in our patient ruled out Klinefelter's syndrome as a potential explanation for the development of male breast cancer.

In addition to Klinefelter's syndrome, several relative risk factors identified in case-control studies suggest a role for androgen deficiency in the development of male breast cancer. These include a history of undescended testes, congenital inguinal hernia, viral orchitis as an adult, testicular injury, infertility, and possibly late puberty [9]. Studies of testosterone in male breast cancer patients have shown slightly increased mean plasma testosterone levels when compared to controls, but the differences have not been statistically significant [10–13]. It is possible that the period of androgen deficiency relevant to the development of breast cancer may occur years before clinically detectable cancer is present. In our patient, a long history consistent with androgen deficiency due to a prolactinoma was present before the development of bilateral breast cancer.

Estrogen excess also has been implicated in the development of breast cancer in men. Obesity, liver disease, high plasma cholesterol, and the presence of gallstones are conditions associated with increased levels of endogenous estrogens that are also associated with an increased risk for the development of male breast cancer [9]. The risk of developing male breast cancer following exposure to estrogens may depend on the duration of the exposure and the age at which it occurs. Estrogen administered to treat prostate cancer often results in gynecomastia, but the incidence of breast cancer is not increased in these elderly patients [14]. Large doses of estrogen given to male transsexuals for purposes of feminization have resulted only in rare case reports of breast cancer [14,15]. Serum estrogen levels have been found to be elevated in male breast cancer patients in several studies [9–11], but not in the largest case-control study [13].

The role of the pituitary hormone prolactin in breast cancer is not well defined. A large body of experimental data has established that prolactin may initiate and promote mammary tumors in rodents [16]. In addition, the tumorigenic properties of estrogen administration in some strains of mice have been found to depend on the presence of prolactin [17,18].

The question of whether prolactin has a role in the development of breast cancer in humans is unresolved. In women, retrospective case-control studies have yielded conflicting data when prolactin levels in breast cancer patients and controls have been compared [19]. In males, elevated levels of prolactin were hypothesized to be the mechanism for the increased risk of breast cancer in men with a history of head trauma found in one study [20]. A subsequent study, however, found no association between head trauma and the development of male breast cancer [9]. Retrospective case-control studies of drugs known to stimulate prolactin secretion have not consistently found an association with breast cancer [9,20]. Three studies of prolactin levels in male breast cancer patients have been performed. Two of these studies found no difference between cases and controls [12,13], whereas the third study found elevated serum prolactin in six of 15 patients and normal prolactin levels in all controls [21].

SUMMARY

The hormonal factors involved in male breast cancer may be complex in their interactions with one another and may act over long periods of time. This is dramatically illustrated in the case presented above, where many years of abnormal endocrine function and a history of prior breast pathology due to the presence of a functioning prolactinoma culminated in the unusual development of bilateral breast cancer in a male patient. It is remarkable that of the three male patients reported to have developed breast cancer associated with a prolactinoma, two have had bilateral disease. In each of these cases, carcinoma of the breast developed years after the surgical treatment of a prolactinoma.

Because the process of carcinogenesis may take place over years and relevant hormonal mechanisms may operate years before detectable tumor is present, it is not surprising that retrospective studies of estrogen, androgen, and prolactin levels in male breast cancer patients have been inconclusive. Useful data have been provided by epidemiologic retrospective case-control studies. These studies suggest that hormonal mechanisms are important in the development of male breast cancer. As is the case with breast cancer in women, the precise nature of these mechanisms remains to be defined. Male breast cancer patients, particularly in the setting of bilateral disease, should be questioned about symptoms of endocrine dysfunction. When these symptoms are present, appropriate endocrine studies should be obtained.

ACKNOWLEDGMENTS

The authors thank Vicky James for assistance in preparing this manuscript.

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